REMARKS

Summary of the Invention

The present invention features a method for determining the prognosis of a patient diagnosed with Alzheimer's disease, neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, multiple infarcts dementia, a prion disease, a pathology of the developing nervous system, a pathology of the aging nervous system, an infection of the nervous system, a dietary deficiency, or a cardiovascular injury. The method is performed by determining the patient's *apoE* allele load, in which the presence of an *apoE4* allele or ApoE4 protein isoform indicates that a patient will respond poorly to a cholinomimetic agent.

Summary of the Office Action

Claims 1, 3, 5-8, 10-14, and 17-20 are pending. Claims 17-20 have been withdrawn from consideration. Claims 1, 3, 5-8, and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, and under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,935,781 (hereinafter "the '781 patent"). These claims are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Serial No. 09/865,753 (hereinafter "the '753 application"). By this reply, Applicant cancels claims 17-20, amends claim 1, and addresses each of the Examiner's rejections below.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 5-8, and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that "the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims" (Office Action, pp. 2-3). Applicant respectfully traverses this rejection.

As was discussed in the previous Reply to Office Action, submitted on April 30, 2003, enablement of an invention, under 35 U.S.C. § 112, first paragraph, "requires a determination of whether the disclosure of the invention, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (M.P.E.P. § 2164.01). The M.P.E.P. § 2164.01 also states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

Further, the Federal Circuit held in *Musco Corporation v. Qualite, Inc.* (790, 41 USPQ2d (Fed. Cir. 1954)):

> A patent's specification must set forth "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112. Section 112 requires only an objective enablement; the invention needs to be sufficiently disclosed through illustrative examples or terminology to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. *In re Marzocchi,* 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971). Although some experimentation on the part of the artisan is not fatal, *Northern Telecom, Inc. v. Datapoint Corp.*, 908

> F.2d 931, 941, 15 U.S.P.Q.2D (BNA) 1321, 1329 (Fed. Cir. 1990). (Emphasis added.)

Finally, in cases in which the Patent Office questions the enablement of a claim:

> [I]t is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), at 370; Emphasis added.

The Examiner argues that claims 1, 3, 5-8, and 10-14 lack enablement because the claims encompass an extremely large genus of disparate neurological disorders, none of which, aside from AD, appear to have any genetic link to apoE (Office Action, pp. 3-5). The Examiner also argues that the specification fails to establish any correlation between *apo*E ε4 allele loads and any neurological disorder other than AD, fails to provide adequate guidance regarding *apo*E ε4 allele loads and therapy, and provides no working embodiments involving non-AD neurological disorders (Office Action, p. 5). Finally, the Examiner states that the prior art clearly teaches that *apoE* allele frequencies do not correlate with most non-AD neurological disorders (Office Action, pp. 5-7). The Examiner argues that the skilled artisan would not reasonably believe that a patient's apoE allele status can be used to establish prognostic outcome in cases of non-AD neurological disorders in light of the uncertainty in the art with respect to the use of apoE in cases that do not involve AD. Applicant respectfully submits that, as is discussed below, even in light of the cited references, the specification enables the full scope of the invention as presently claimed, and assertions to the contrary are, to date, insufficiently supported.

Applicant's Specification Teaches, and the Declaration of Judes Poirier Confirms, the Enablement of the Present Invention

A patent specification meets the enablement requirement of 35 U.S.C. § 112, first paragraph, if one skilled in the art can make and use the invention without undue experimentation (see *In re Wands, supra*). In the present case, Applicant's specification clearly teaches that a patient's *apoE* allele load can be used to determine their prognostic outcome, regardless of the patient's specific neurological disorder (i.e., the patient can be an AD or a non-AD patient). The specification states that "the observation regarding apoE allele load and drug therapies can be generalized to non-AD neurological diseases because the underlying mechanism altered by the apoE allele load is not AD-specific" (see page 11, line 23, through page 12, line 1, of the specification). Applicant observed a marked loss of neurons, for example, cholinergic neurons, and a reduction in neuronal choline acetyltransferase (ChAT) activity and choline levels in *apoE4* carriers versus *apoE3* carriers (see page 11, lines 17-22, of the specification). Applicant recognized that this loss of neurons and neuronal activity was directly related to defects in apoE4 protein function and that this defect occurred regardless of the patient's specific neurological disorder. Based on this discovery, Applicant tested and verified the belief that a patient's *apoE* allele load can be used to determine their prognostic outcome, regardless of the specific neurological disease (i.e., the patient can be an AD or a non-AD patient). Therefore, practicing the method of present claim 1 simply requires determining the *apoE* allele load of a patient already diagnosed with one of the recited neurological disorders; the presence of an *apoE* ε4 allele or an ApoE4 protein isoform indicating a poor prognosis for the patient (see, e.g., page 10, lines 20-22, and page 11, line 23, through page 12, line 4). Because all of these steps can be easily performed using well-defined techniques described in, e.g., the specification (see, e.g.,

page 12, line 18, through page 16, line 21), and known in the art, Applicant submits that practicing the method of present claims 1, 3, 5-8, and 10-14 would not require undue experimentation, and therefore, the specification satisfies the requirements for enablement.

The Examiner questions the enablement of the present claims, stating that the claims are directed to several neurological disorders that "fail to share any genetic linkages or biochemical mechanism with those of late onset AD and *apoE* allele frequency" (Office Action, p. 4). For this reason, "the skilled artisan would not consider it reasonable to assert that the apoE allele frequency in all these various disorders, many of which do not directly involve Apo E-regulated transport and internalization of cholesterol and phospholipids, would be predictive of therapeutic responsiveness and clinical outcome" (Office Action, p. 4). Applicant respectfully disagrees.

Applicant has repeatedly pointed out that the method can be broadly applied to patients diagnosed with AD and non-AD neurological disorders because a patient's *apoE* genotype is a determinative factor in the general neuronal health of that patient and is predictive of the general state of neurons in the patient (i.e., the relative health or fragility of neurons). Further, the prognostic method does not require knowledge of the underlying mechanism of the recited neurological disorders. Therefore, the method of present claims 1, 3, 5-8, and 10-14 can be successfully used in patients diagnosed with wide and disparate neurological disorders (see page 11, lines 17-22, of the specification).

This is clearly demonstrated by evidence provided in the Declaration of Judes Poirier, filed on April 30, 2003, which exemplifies the claimed invention in patients diagnosed with the non-AD neurological disorders Parkinson's disease (PD), multiple sclerosis (MS), and stroke, respectively (see, e.g., pp. 2-4 of the Poirier Declaration). The findings presented in the Poirier Declaration with respect to PD and MS demonstrate that carriers of the *apoE4* allele showed

poorer prognosis following treatment than PD and MS patients that do not carry the *apoE4* allele (see pp. 2-3 of the Poirier Declaration). These neurological disorders clearly evince distinctly different pathological determinants and etiologies than that of AD, and yet, the results clearly demonstrate that apoE can be used as a marker of prognostic outcome in these patients. In the case of stroke, the Poirier Declaration discloses that the speed of the patient's recovery from a stroke incident and the duration of their rehabilitation was not negatively impacted by carrying an *apoE4* allele (see p. 4 of the Poirier Declaration). Applicant surmises that this seemingly contrary result simply suggests that a patient's *apoE4* status correlates with some but not all aspects of stroke prognosis and does not correlate with those aspects measured. In the interest of expediting prosecution of claims 1, 3, 5-8, and 10-14, Applicant has amended claim 1 to remove stroke from among the non-AD neurological disorders listed. However, the M.P.E.P. § 2164.08(b) is clear:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E. I. du Pont de Nemours Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

Applicant has clearly confirmed that the method of present claims 1, 3, 5-8, and 10-14 can be performed successfully in both AD and non-AD patients, and that no undue experimentation is required to determine the operability of the presently claimed embodiment. For this reason, Applicant submits that enablement of the present claims has been demonstrated.

Applicant is not Required to Provide Working Embodiments for All Neurological Disorders Recited in Claim 1

The Examiner states that "[t]he disclosure fails to provide any working embodiments involving non-AD neurological disorders" (Office Action, p. 5). Even though Applicant has not exemplified the method for all of the recited neurological disorders, this is not required. The case law is clear that enablement does not require absolute predictability for all possible embodiments of a claimed method, nor is Applicant required to provide a working example for each embodiment if the skilled artisan will be able to practice the invention without an undue amount of experimentation (*In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). The law only requires that the specification in combination with the art provide a description that allows a reasonable number of species falling under the claim to be made and used without undue experimentation (*In re Wands, supra*). Applicant has demonstrated the success of the method of claim 1 in patients diagnosed with both AD (described in the specification) and non-AD neurological disorders (PD and MS; described in the Poirier Declaration). Therefore, a reasonable number of species can be made and used without undue experimentation and the *Wands* standard has been met.

Furthermore, as is discussed above, the first paragraph of 35 U.S.C. § 112 "requires nothing more than objective enablement." *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). For this reason, Applicant does not need to provide a teaching of efficacy for each and every neurological disorder recited in claim 1. Rather, the specification must simply teach how to make and use the invention so that the skilled artisan can practice the invention without undue experimentation. Applicant's specification clearly teaches the

usefulness of the presently claimed method in patients diagnosed with the neurological disorders recited in claim 1, particularly in patients with AD, and the evidence described in the Poirier Declaration provides additional confirmation that a patient's *apoE* status is reasonably predictive of a patient's outcome following diagnosis with PD or MS, two very disparate neurological disorders. Thus, one of ordinary skill would reasonably extrapolate the experimental findings to the prognosis of the other recited neurological disorders, not just those tested. Moreover, the undisputed positive results presented in the Declaration of Judes Poirier, taken in light of the cited references, discussed below, would not lead the skilled artisan to question the usefulness of measuring *apoε*4 allele loads, as is suggested by the Examiner, because the evidence clearly demonstrates the usefulness of *apoE* determination for prognostic purposes.

To the extent that the Examiner suggests that there is a requirement for precise *a priori* predictability without recourse to any experimentation, that position is without legal support. Cf. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) ("[t]hat some experimentation is necessary does not preclude enablement"). The proper test of enablement in such a situation is whether the disclosure "adequately guide[s] the skilled artisan to determine, without undue experimentation, which species among all those encompassed by the...[claims] possess the disclosed utility." See *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

The Examiner's "test", in the absence of illustrative examples, would apparently require the skilled artisan to be able to determine for which of each and every neurological disorder *apoE* allele loads can be used to produce a determination of prognostic outcome. This is not the *Vaeck* test. The *Vaeck* test recognizes proper enablement where the skilled artisan is able to determine, once the methodology is established for one neurological disorder and based on

reasonable experimentation, whether the same methodology is effective for other neurological disorders.

The high level of skill in the art and the extensive knowledge available to one of skill in the art, coupled with the teachings of the present specification adequately guide the skilled artisan to determine, after selection and without undue experimentation, for which neurological disorder encompassed by the claims *apoE* allele load determination possesses utility. Performing routine and well-known steps cannot create undue experimentation even if it is laborious. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404; *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218-219 (CCPA 1976). Therefore, contrary to the Examiner's position, practicing the method of present claims 1, 3, 5-8, and 10-14 would not require undue experimentation by the skilled artisan to practice the claimed invention in a manner commensurate in scope with the claims.

Applicant Does Not Need to Establish a Correlation Between the Neurological Disorders Covered by the Claim Language to Enable the Present Claims

The Examiner argues that "[t]he declaration and disclosure fail to provide a common biochemical nexus between the sundry neurological disorders covered by the claim language" (Office Action, p. 9). This also is clearly not the standard for establishing enablement of a claimed invention. Applicant need not establish the biochemical underpinnings of each disorder, nor how each disorder relates to the other, to enable use of the method of present claim 1. Applicant need only teach how to make and use the claimed invention without requiring undue experimentation (*In re Wands*, *supra*); a standard Applicant has clearly met.

Nonetheless, Applicant again points out that the mechanistic commonality conferred by the presence of an *apoE4* allele is the relative fragility of the neurons in patients carrying the allele. This fragility in *apoE4* carriers makes their prognosis worse when they are challenged with a neurological disease. Therefore, the method of present claims 1, 3, 5-8, and 10-14 can be successfully used in patients diagnosed with wide and disparate neurological disorders without the requirement for understanding the cause of the recited neurological disorders; all that is required is knowledge of the patients' *apoE* status (see page 11, lines 17-22, of the specification).

Enablement of the Present Claims Does Not Require Guidance Pertaining to the Correlation of apoE Allele Loads and Treatment

The Examiner states that "*apo*E ε4 allele load in AD patients is reasonably predictive of patient responsiveness to cholinomimetic therapy...[h]owever, the disclosure fails to provide any guidance pertaining to other suitable therapeutic compounds and the predictive value of measuring the *apoE* allele load in these settings" (Office Action, p. 5). Because the present claims do not require treatment of the diagnosed patient, knowledge of therapeutic compounds that are suitable for treating patients having one or more *apoE ε4* alleles and one or more of the recited neurological disorders is not required to practice the method of present claims 1, 3, 5-8, and 10-14. As is discussed above, the specification clearly teaches that a patient's *apoE* genotype is a determinative factor in the general state of neurons in that patient (see, e.g., page 11, lines 17-22, of the specification). Thus, the neurons of patients that carry one or more *apoE4* alleles have a reduced ability to respond to drug therapies, in general, than do patients that do not carry the *apoE4* allele. Therefore, patients that carry one or more *apoE4* alleles demonstrate a poorer prognosis following diagnosis with a neurological disorder due to the lack of neuronal

responsiveness. This lack of neuronal responsiveness occurs not only in AD patients treated with cholinomimetics, as is described in the specification on page 28, line 13, through page 31, line 18, but also in PD patients treated with levodopa, a neurotransmitter precursor, and in MS patients treated with interferon β-1B, a cytokine (see the Declaration of Judes Poirier, pp. 2-3). Therefore, it is not necessary to establish a correlation between *apoE* allele loads and a patient's neurological condition in order to practice the presently claimed method. Accordingly, Applicant need not provide guidance to the skilled artisan, with respect to treatment methodologies, to enable the skilled artisan to practice the method of claims 1, 3, 5-8, and 10-14.

The Documentary Evidence Cited by the Examiner Does Not Support the Present Enablement Rejection

As required by *Marzocchi*, to reject a claim based on lack of enablement, the Patent Office must provide acceptable reasoning or evidence that is inconsistent with an Applicant's assertion that a claimed product or process is enabled (*In re Marzocchi, supra*). Here, the Examiner has provided Morris et al., which further cites Saunders et al., Pickering-Brown et al., Royston et al., Martins et al., and Wisniewski et al., for the proposition that "[n]o changes in APO E allele frequencies were found in presenile AD, Parkinson's disease with or without dementia, or in Down's syndrome" (Office Action, pp. 5-6). Applicant noted in the previous Reply to Office Action, and reiterate here, that Morris et al. and the other cited references merely describe attempts that were made to uncover a relationship between *apoE* genotype and the ability to diagnose or even forecast the onset of a particular neurological disease. The present claims are not directed to the diagnosis of neurological disorders by determining a patient's apoE status, but rather, the claims are directed to a method for determining the prognosis of a patient already diagnosed with one of the neurological disorders recited in present claim 1 based on their

apoE status. None of the cited references suggest any uncertainty with regard to the use of *apoE* in a prognostic capacity. As the cited references do not convey any uncertainty with respect to the use of *apoE* in this capacity, Applicant again argues that the references are not germane to the claimed invention.

Regardless, the cited references do not suggest any uncertainty with respect to the use of *apoE* for determining prognostic outcome following diagnosis of a patient with a neurological disorder. As required by *Marzocchi*, the Examiner must explain *why* he doubts the objective truth of Applicant's statements that the use of *apoE* for determining a patient's prognostic outcome is enabled, when only evidence that suggests uncertainty with respect to the use of *apoE* in a diagnostic capacity, a use which is distinctly different from the use of *apoE* in a prognostic capacity, has been presented (*In re Marzocchi, supra*).

In addition, *Marzocchi* states:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), at 369.

In response to the Examiner's rejection of claims 1, 3, 5-8, and 10-14, Applicant has provided such suitable proofs indicating that the teaching of the specification is truly enabling. As is discussed above, Applicant's specification teaches the use of *apoE* in a prognostic capacity in cases of AD and non-AD neurological disorders. Further, the Poirier Declaration, also discussed above, provides additional evidence of the truth of Applicant's statements and clearly

demonstrates the enablement of claims 1, 3, 5-8, and 10-14 for neurological disorders other than AD. Accordingly, Applicant submits that the skilled artisan would not question the usefulness of the method of present claims 1, 3, 5-8, and 10-14, even in light of the references cited by the Examiner, and furthermore, the burden of proof standard set forth in *Marzocchi* has not been met by the Examiner.

Summary

Applicant's specification clearly teaches how to make and use the method of present claims 1, 3, 5-8, and 10-14 without undue experimentation. The methods can be used to determine either an AD or a non-AD patient's prognosis. The methods are easy to practice; all that is required is a determination of a patient's *apoE* genotype. Furthermore, based on the specification as filed and the examples described in the Poirier Declaration, the present claims are not unduly broad, bear a reasonable correlation to the full scope of the claimed invention, and are fully enabled. Accordingly, Applicant respectfully requests that the rejection of claims 1, 3, 5-8, and 10-14 be withdrawn.

Rejection for Obviousness-Type Double Patenting

Claims 1, 3, 5-8, and 10-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of the '781 patent. The Examiner states:

> The claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders and *apo*E allele load determinations while the claims of the '781 patent are directed toward patient prognostic protocols involving patients with cognitive impairments, which are caused by CNS pathologies. Thus, the claims of the '781 patent fall

> within the scope of the claimed invention and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent. (Office Action, p. 10.)

In response to the obviousness-type double patenting rejection, Applicant will submit a terminal disclaimer, if necessary, to overcome the rejection once otherwise allowable subject matter has been determined.

Rejection for Provisional Obviousness-Type Double Patenting

Claims 1 and 3-15 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of the '753 application. This rejection can be withdrawn in light of the abandonment of the '753 application on July 9, 2004.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested. If the Office does not concur, a telephonic interview with the undersigned is hereby requested.

Also enclosed is a Petition to extend the period for replying for four months, to and including August 13, 2004, and a check for the fee required under 35 U.S.C. § 1.17(a).

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 13 August 2004

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